Modification of Potassium-Mortality Relationship by Ethnicity and Race: Solving the Puzzle

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In health, serum potassium (K) concentration is regulated by mechanisms that operate both in the short term and long term. In the short term, the major regulatory factors are the acid-base status, catecholamines, and insulin; in the long term, regulation of serum K concentration is by the kidney, the mineralocorticoid, and glucocorticoids. The colon assumes a role in maintaining K homeostasis in the anephric state [1]. In anephric patients, dietary K intake becomes a major determinant of serum K. Dietary K intake is influenced, at least among people not on dialysis, by ethnicity and race [2]. Departures from the homeostatic range of K regulation are associated with all-cause mortality. However, what is less clear in the anephric state is whether ethnicity and race modify the relationship that exists between serum K and mortality.

In this issue of the American Journal of Nephrology, Taehee et al. [3] report among >100,000 dialysis patients, the modification of odds of hypokalemia and hyperkalemia by race and ethnicity. Furthermore, over a median follow-up of 1.3 years, they report the modification of the hazards of all-cause mortality due to hypokalemia and hyperkalemia by race and ethnicity. Specifically, with whites as a reference group, the odds of hyperkalemia were 32% higher in Hispanics but 42% lower in blacks. Conversely, compared to whites, the odds of hypokalemia were 63% higher in blacks and 11% lower in Hispanics. Hyperkalemia was associated with increased all-cause mortality in blacks and whites but not in

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Hispanics. In contrast, hypokalemia was associated with increased all-cause mortality in Hispanics but not among blacks or whites. Despite a large number of cardiovascular events, there was no modification by race and ethnicity of the association of serum K patterns and cardiovascular mortality.

From a physiological perspective, these findings are complex and puzzling. Specifically, if these relationships are causally related, one has to wonder what the causes might be. These causes could be related to 2 factors: diet or the distribution of K within and outside the cell. We will attempt to unravel the puzzle by discussing each of these 2 mechanisms.

Dietary K Intake

If Hispanics had a higher dietary K intake compared to blacks and whites, hypokalemia in Hispanics may signal a greater severity of illness. The community-based, National Health and Nutrition Examination Survey 2009-2010 data for men and women 20 years or greater showed mean K (in mg/day) intakes of 3,288 in whites, 2,695 in blacks, and 3,105 in Hispanics [2]. The corresponding intakes among women were 2,469 (whites), 2,101 (blacks), and 2,317 (Hispanics) respectively. Accordingly, at least in the general population both among men and women, Hispanics have a dietary K intake that is similar to that of whites [2]. For both men and women, blacks on the other hand have a lower dietary K intake. Since whites and Hispanics have a similar K intake, yet have a different relationship of serum K concentration and mortality, this cannot be the sole explanation for the higher observed mortality. Unless dialysis modifies the dietary intake of K among races - for which we have little evidence - the dietary hypothesis remains unsupported.

Distribution of K within and Outside the Cell

It should be noted that in the study of Taehee et al. [3,] the all-cause mortality was adjusted for net protein catabolic rate, which is a proxy for dietary protein intake. Since both the dietary protein intake and the dietary K intake are highly correlated, what may be measured in the all-cause mortality is not an

association of K concentration with outcomes but K concentration adjusted for intake (or K-sensitivity) with outcomes.

The distribution of K within and outside the cell is influenced by many factors such as the acid-base status, catecholamine concentrations, and insulin. Homeostasis model assessment-estimated insulin resistance (HOMA-IR), a validated measure of insulin resistance, is the highest in Hispanics (3.08) compared to that in blacks (2.90) and whites (2.76) [4]. Thus, it is possible that race and ethnicity may modify the ability of insulin to drive K within the cell, just like it does for glucose. In the study of Taehee et al. [3], the mean K concentration was 4.58 mEq/L in Hispanics, 4.43 in whites, and 4.31 in blacks. Like HOMA-IR, the K concentration was the highest among Hispanics. We may hypothesize that resistance to the effect of insulin in driving glucose within cells may be similar to the effect of insulin in driving potassium within cells. However, mechanistic studies of insulin infusion in people with (n = 12) and without diabetes (n = 32) performed in a metabolic ward illustrate that although glucose disposal rate is impaired in diabetes, cellular K uptake rate is similar in the 2 groups [5]. Furthermore, no relationship is seen between the K uptake rate and the glucose disposal rate ($r^2 = 0.016$). The sensitivity of K and glucose to insulin is therefore on 2 distinct pathways that may not share much in common. Whether K-insulin relationship is modified by race and ethnicity remains unknown. At present, therefore, this hypothesis remains unsupported.

It has now long been known that a rapid injection of epinephrine causes a short-lived increase in K due to alpha-adrenergic stimulation of the liver followed by a more prolonged drop in K due to skeletal muscle uptake as a result of beta-adrenergic stimulation. Beta-adrenergic stimulation is known to lower plasma K levels by increasing cellular K uptake independent of venous pH, plasma bicarbonate, and plasma glucose. These effects are particularly noticeable during exercise [6]. For example, exercise increases catecholamine levels and plasma K; after the termination of exercise plasma catecholamine and K, both fall. In the setting of beta blockade, the rise in K is greater and more sustained after the termination of exercise [6]. In contrast, in the setting of alpha-blockade, the rise in K is lowered during

exercise and throughout recovery [6]. In the study of Taehee et al. [3], although all measurements of K were in the resting state, the use of beta-blockers and alpha-blockers was not reported. Whether the K-catecholamine relationship is modified by race and ethnicity remains unknown.

What if K-Mortality Link Is Not Causal?

So far, we have considered that the link between K and mortality is causal in nature. This is because it is commonly believed that hyperkalemia or hypokalemia predispose to cardiac arrhythmias particularly in a predisposed dialysis population with cardiovascular disease. Predisposing cardiovascular disease risk factors of particular importance in dialysis patients are cardiac chamber hypertrophy, chamber enlargement, and coronary artery disease. Despite a large number of cardiovascular deaths, Taehee et al. [3] did not find an association between hypo- or hyperkalemia and cardiovascular mortality. The true cause of death may not be reflected accurately in death certificates, so a lack of association of K with cardiovascular mortality could be a false negative finding. At least some evidence that Taehee et al. [3] may have missed the signal comes from a recent study among people not on dialysis and free of cardiovascular disease at baseline [7]. In this cohort, serum K $\geq$5.0 mEq/L was associated with both cardiovascular death and non-cardiovascular death [7]. However, this study was limited to people with less intense kidney disease and no cardiovascular disease at baseline. On the other hand, if the true state was no excess in cardiovascular mortality - the results of the study would then accurately represent this truth. Thus, it would follow that low or high potassium concentrations are reflections of departures from health; in other words, hypokalemia or hyperkalemia may reflect the severity of disease. Thus, the K-mortality relationship may not be causal.

Despite considering many of the potential causes of the relationships of K and all-cause mortality, we still are left wondering why the relationships of patterns of K and all-cause mortality are modified by race and ethnicity. Taehee et al. [3] used only baseline K concentration to evaluate its association with outcomes. One may want yet another cohort study to evaluate the change from baseline in K

concentration and its association with mortality and its causes. Even if such a study were performed, the causal pathway will still be obscure.

In summary, this large epidemiological study of Taehee et al. [3,] which illustrates the modification of K mortality association by race and ethnicity, has generated yet another question. More questions than answers - this situation is so common in our field - questions whose answers may need mechanistic studies or a randomized trial. One strategy such a trial may test is to correct K concentration depending on its level. Among those with hyperkalemia, we may use agents that bind K in the gut and among those with hypokalemia to supplement dietary K intake. The study of Taehee et al. [3] informs us that if such a trial were to be conducted then race/ethnicity should be considered a stratification variable in the study design or a confounding variable in the analytical plan. For now, the puzzle is yet to be solved. The provenance of the solution may exist not in another cohort study, but in a mechanistic study or an interventional trial.

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